MULTI-ENGINEERING OF MICROBIAL CYTOCHROME P450 ENZYMES

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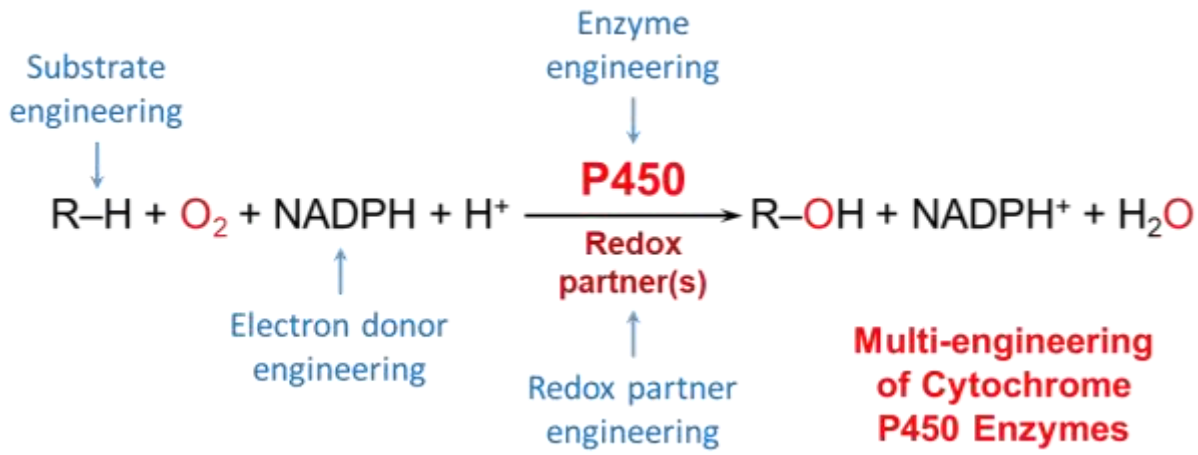
Selective oxidation of unactivated C–H bonds remains a central challenge in synthetic chemistry. Cytochrome P450 enzymes, a superfamily of ubiquitous hemoproteins, represent the nature's primary solutions to overcome this challenge. As promising biocatalysts for practical applications in pharmaceutical, biotechnological and chemical industries, P450 enzymes have attracted a wealth of attention due to their great versatility in catalyzing diverse oxidative reactions (*e.g.*, the sp^3 C–H hydroxylation and the sp^2 C=C epoxidation) on structurally complex and heavily functionalized substrates in regio- and/or stereoselective manners. However, wild type P450 enzymes usually show suboptimal activity, low stability, and narrow substrate spectra, which have significantly limited their broader applications. A typical P450 reaction system includes a P450 enzyme as the central catalyst, a substrate to be oxidized, redox partner proteins for electron transfer, NAD(P)H as the electron donor, and O_2 as the oxidant. In the past five years, we have made significant progresses on enzyme engineering, substrate engineering, redox partner engineering, and electron donor engineering for a number of microbial P450 enzymes. These multi-engineering efforts have generated useful engineered P450 catalytic systems for bio-production of pharmaceuticals, chemical intermediates, and biofuel molecules.



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